Innovative Reformulation of a Complex, High-Drug-Load, Modified Release Dosage Form With Reduced Dosing Frequency

Myke Scoggins, Ph.D. - Director, Product Development at Recro
Richard Sidwell, Ph.D. - Vice President and Chief Scientific Officer at Recro
Ryan Crawford - Process Development Scientist at Freund-Vector

Formulation Development

The Reformulation Challenge

- High drug loads
- Complex dissolution profiles
- Two incompatible APIs

The Recro/Freund-Vector Solution

- Efficient, fast proces
- One-pot coating method
- Modular and tunable dosage strength and release rates
- High-quality drug product

BACKGROUND

Reduction in a drug's dosage regimen offers greater patient convenience, better adherence, and the potential for lower side effects. Therefore, clients often ask for help reformulating their multidose oral therapies into once- or twice-daily dosage forms. Multiparticulate capsules are a go-to option for such tasks because, with multiple populations of beads, the API content and release rates can be easily adjusted.

Frequently, Wurster coaters are used to make such beads. However, the manufacturing process takes time and if the drug load per bead is high, multiple coatings may be necessary — taking even more time. And in the worst-case scenario, the final drug product may be so large that it becomes difficult for the patient to swallow.

In this case study, Recro® resolved these concerns by applying a different technology to create a high-drug-load, twice-daily dosage form much more efficiently than a spray coater could.

PROBLEM

A new customer asked Recro to reformulate an immediate-release oral solid dosage form to an extended-release product with a complex release profile. While the original dosing was 3x/day, the new formulation was to be twice daily. The product contained two chemically incompatible APIs with different dissolution profile requirements. Each API required both immediate and modified release components.

This reformulation was a challenge. The product had a high drug load and the pharmacokinetics (PK) required were both specific and elaborate. Multiple feasibility PK studies were necessary. While being tunable for its dissolution profile, the new formulation also had to be modular to make dosage strength and immediate-release to modified-release ratios easily adjustable. Additionally, the APIs would have to be kept physically separate because of their instability in the presence of each other and the differences in the required dissolution profiles.

SOLUTION

Recro quickly realized matrix and bilayer tablets would be difficult to fine-tune, while a mini-tablet format would be impractical. The team decided the best option to fulfill the complicated PK requirements of this reformulation was a multiparticulate capsule. Each bead type would need to be developed with different amounts of various polymers to produce the release rates required to achieve the specified pharmacokinetics. By varying the choice and amounts of polymer and the quantities of the four pellet populations in each capsule, the dosage strength and release rates would be modular and tunable.

But what process could be used to form pellets with large API loads? For the typical Wurster coating process, a solution or suspension of the drug and a film-forming agent are sprayed onto a substrate such as a sugar sphere — creating a high-quality coating. However, it is a long process and achieves a limited drug load. To achieve high drug loads, it can be necessary to split the batch into sublots for additional coating. These were significant drawbacks for this project which required four separate high-drug-load pellet populations.

Instead, Recro opted for a powder layering method using Freund-Vector's Granurex® Rotary Granulation process. In this process, a core substrate is spun around on a conical rotor while powdered API and a liquid binder solution are separately sprayed in from the sides. The benefits of this method are that it typically requires little binder, quickly applies large quantities of API to each pellet, and produces a reliably uniform particle. In this case, the Freund-Vector Granurex® GX-40 conical rotor's powder layering function greatly simplified and accelerated the production of the four high-API-load pellet populations required.

To finish, Recro scientists took advantage of the solution/suspension coating mode from the Granurex® to add a high-quality functional polymer coating to make the modified release pellet population. While this could have been completed as a separate Wurster process, the one-pot method was much more efficient than switching to a different type of equipment where another set of processing parameters would have to be developed.

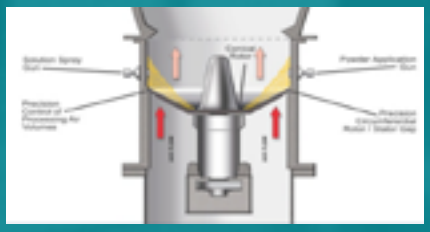
OUTCOME

A comparison between the Wurster and Granurex® conical rotor powder layering processes is shown in the table. The powder layering process:

- Enabled significantly higher drug loading than a typical Wurster process
- Loaded beads with API quickly, achieving a 400% weight gain in 8 hours at commercial scale
- Achieved good uniformity, as shown by the narrow particle size distribution

The Freund-Vector GX Conical Rotor

The highly flexible Freund-Vector GX conical rotor can be used for spherical granulation, dry powder layering, and Wurster-like solution/suspension coating, either singly or in combination for fast, efficient processing.



About Powder Layering

In this process, the API powder isdispersed directly onto the core material (sugar/starch or microcrystalline cellulose spheres, API containing granules, etc via a powder gun port. Sprayed binder solution makes the powder cumulatively adhere to the core.

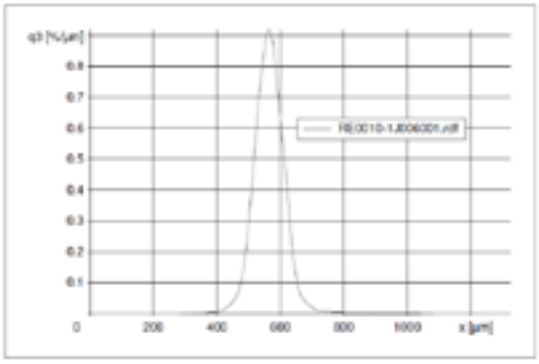
Advantages:

- Adding API as a powder rather than dissolving or suspending it into a liquid spray saves time
- A 500% weight gain can be added in a relatively short time
- The particle size distribution (PSD) remains very narrow even after the high weight gain is applied

Comparison of attainable drug loading in Wurster vs. powder layering processes

	Wurster Process	Powder Layering Process
Potency of Drug Applied	75% w/w (of solids in suspension)	100% (neat API)
Amount of Binder Needed	(Included in suspension)	10% of drug mass
Possible Weight Gain for a Single Pass	4x core weight	6x core weight
Maximum IR Drug Load	(75 x 3/4) = 56%	(100-10) x 5/6 = 74%
Weight of MR Coating vs. Drug	50%	50%
Maximum MR Drug Load	75/2 = 37%	99/2 = 49%

(A)



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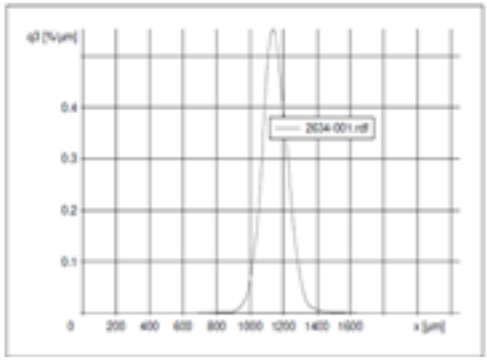

Uncoated 30/35 mesh sugar spheres (A) and coated beads (B) showing a narrow particle size distribution and a high degree of uniformity.

CONCLUSION

Recro's industry-leading experts provided an adaptive solution to a multifaceted formulation challenge demanding a complex oral solid dosage form with specific dissolution profiles and pharmacokinetic requirements. As pioneers in the development of extended release dosage forms, the Recro team has many years of experience in complex oral solid dosage development and manufacturing. With the help of the sophisticated, high-performance Freund-Vector Granurex® equipment, the team exceeded client expectations in a complicated reformulation project.

About Recro

Recro® provides oral solid dosage form development, regulatory support, clinical and commercial manufacturing, and packaging and logistics services to the global pharmaceutical market. Specializing in modified release oral solid dose and DEA controlled substances, Recro has the experts to deliver our clients' most complex pharmaceutical development and manufacturing projects in our best-in-class facilities, totaling 120,000 square feet. For more information about Recro's flexible CDMO solutions, visit recrocdmo.com.

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